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Multiphase flow processing in microreactors combined with heterogeneous catalysis for efficient and sustainable chemical synthesis

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ABSTRACT

The convergence of continuous flow chemistry and microreactor technology creates numerous possibilities towards the development of an efficient and sustainable chemical synthesis. In this field, the combination of heterogeneous catalysis and multiphase flow processing in microreactors represents an important approach. This review presents a summary of the recent progress on the utilization of wall-coated and packed-bed microreactors for carrying out heterogeneously catalyzed gas-liquid and liquid-liquid reactions, with a focus on the microreactor operation principles and selected reaction examples with promising application potential. Finally, an outlook on the future development trends is provided.

1. Introduction

The petrochemical, fine chemicals and pharmaceutical industries, are striving for developing more sustainable chemical processes and products with high efficiency, in order to well address the ever-increasing global concern on the environmental protection and intensive worldwide competition in the existing or new market areas for the maximized economic benefits [1,2]. This has attracted numerous research attentions over recent years in both academia and industry on the development of novel synthetic strategies using green chemistry concepts and the corresponding key-enabling chemical process technologies for their promising application. In this field, many researches have been driven by the use of those widely accepted green chemistry and green engineering principles for the design of environmentally acceptable processes and products [3–6].

Along this research line, the convergence of continuous flow chemistry and microreactor technology as two rapidly expanding research areas has shown its great effectiveness for an efficient and sustainable chemical synthesis [7–14]. The switch from batch to continuous flow processes has been an important paradigm change in chemical synthesis, which is especially relevant to the fine chemicals and pharmaceutical industries where there is a dominant use of conventional batch reactors (e.g., flasks and stirred tank reactors) for laboratory development and/or industrial application, due to their flexibility, easy use and established experience in operation. It is now generally acknowledged that running chemical synthesis in continuous flow mode usually offers much better control over reaction/process parameters (e.g., mixing, heating, multi-step operation, throughput) and product properties (e.g., product quality and consistency), and therefore has been listed as one of the top key research areas for the fine chemicals and pharmaceutical industries [15]. For the petrochemical and bulk chemical industries, although the adoption of continuous flow processing has been a common practice, the earlier-stage laboratory investigations usually involve (less efficient) batch processing and there is also an urgent need in the implementation of process intensification for uplifting those running processes and for the design of new, sustainable processes and products [2,16]. Microreactor technology as a typical method of process intensification holds great promises for enabling and accelerating the discovery of flow chemistry towards highly efficient and more sustainable chemical synthesis, primarily due to numerous benefits along with the miniaturization of reactor dimensions to (sub-)millimeter scale [8–10]. By confining reagent flow in reaction microchannels, substantial transport intensification (e.g., enhanced heat/mass transfer), precise process control (e.g., regular flow pattern, fast response and nearly uniform temperature distribution) and reliable operation under novel process windows (e.g., under elevated temperatures and pressures, solvent-free conditions or explosive regime) are easily attainable [11–13]. These merits create unique opportunities to greatly improve the existing chemical routes (e.g., in safety enhancement, waste minimization and efficiency maximization), and enable green chemical transformations using novel and efficient synthetic protocols (an area that is especially promising when combined with the use of environmentally friendly reagents).

Currently, the use of microreactors as a promising continuous flow reactor concept for conducting a rich variety of chemical syntheses is in full swing, with its inception around 1990s. This review aims to provide

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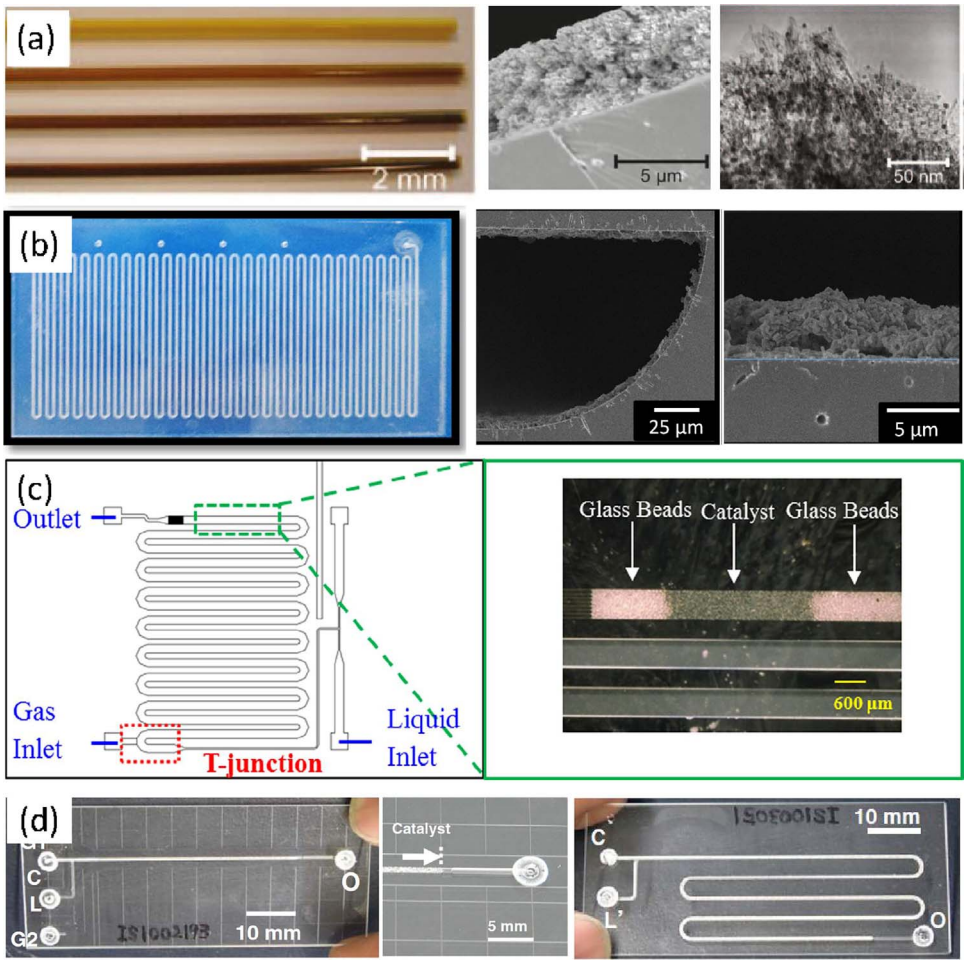


Fig. 1. Combination of microreactors with solid catalysts. (a) Fused silica capillary microreactor coated with 0, 1.1, 2.7, 5.7 wt% Pd/γ-Al_2O_3 catalysts (left) and SEM image of the coated γ-Al_2O_3 layer (middle) and TEM image of Pd nanoparticles (black dots) over γ-Al_2O_3 support (right) [32]. Reproduced with permission from Wiley. (b) Glass microreactor chip with a silicalite coating (left) and SEM images of the chip with a Pd/silicalite coating (middle and right) [33]. Reproduced with permission from Elsevier. (c) Schematic of a silicon-glass packed-bed microreactor (left) and picture of the reaction microchannel packed with bimetallic Au-Pd/TiO_2 catalyst and glass beads before and after the catalyst bed (right) [34]. Reproduced with permission from Elsevier. (d) The first single-channel glass microreactor chip with 40 mm long packed bed (left) and the bottom of the packed catalyst bed thereof (middle) and the second single-channel glass microreactor chip with 200 mm long packed bed (right) [35]. Reproduced with permission from Elsevier.

a summary of the recent progress on the combination of multiphase flow processing and heterogeneous catalysis in microreactors towards an efficient and sustainable chemical synthesis (a very promising area for the valorization of microreactor technology in conjunction with continuous flow chemistry), as further supported by the following considerations:

i) Multiphase (typically gas-liquid, liquid-liquid) systems are involved in many chemical transformations of high importance to the chemical industry, such as liquid-phase hydrogenation using H_2 [16], oxidation of organic substrates like alcohols using H_2O_2 or O_2 as a green oxidant [17], synthesis of biofuels using biphasic transesterification [18]. A superior reaction performance herein entails a precise control over multiphase contact in order to obtain a high interfacial area and subsequently desirable mass transfer and reaction rates, which is usually hard to achieve in conventional (batch) reactors especially on a large scale. In this respect, significant transport intensification under precise process control readily available in microreactors can provide truly innovative solutions [19].
ii) Heterogeneous catalysis represents one of the key tools for increasing the sustainability of the above transformations mentioned in i) [16–18], e.g., by simplifying the product work-up, allowing easy catalyst separation and reuse, when compared with homogeneous catalysis. The incorporation of active, selective and stable solid catalysts (e.g., in the form of immobilized coatings or micrometer-sized powders) into microreactors brings additional benefits in providing high specific surface areas to catalyze the usually challenging tri-phasic (i.e., gas-liquid-solid or liquid-liquid-solid) reactions [20].

This review is organized by first introducing the two main types of microreactors for performing heterogeneous catalysis in multiphase systems (i.e., wall-coated and packed-bed microreactors), followed by a detailed discussion on the basic operation principles and selected reaction examples with promising application potential. Finally, the future research trends and application prospects are envisaged. It should be pointed out that the latest updates on the potential of microreactor flow processing in a much broader context have been summarized in some literatures, for instance, when it comes to dealing with general types of reactions (being non-catalytic, homogeneously or heterogeneously catalyzed) [7,10,12,13,20–24] and specific types of reactions like oxidation [25–27]. Although these literatures have covered various aspects of the current review to some extent, they do not provide a clearly separated and more in-depth overview of solid-catalyzed multiphase reactions in microreactors, especially from a combined green chemistry and engineering point of view.

As its name implies, microreactors in an earlier stage were typically composed of fluidic microchannels (with characteristic dimension in the sub-millimeter range, e.g., 50–1000 μm) made by microfabrication techniques on substrates like silicon and glass, and usually had a chip- or plate-based format [16,28]. With the rapid expanding of flow chemistry community, affordable and readily available capillary tubings (often based on perfluorinated polymer, fused silica and stainless steel) as another type of microreactors are becoming increasingly popular [8]. Now, continuous flow reactors with characteristic channel dimensions on the millimeter scale (e.g., 1–3 mm) are also often referred to as microreactors [22], although they might be better described

Table 1
An overview of multiphase reactions performed in wall-coated microreactors.

Entry	Reaction	Microreactor[a]	Catalytic coating	Main coating procedure	Operational conditions	Results	Reference
1	Hydrogenation of 3-methyl-1-pentyn-3-ol (Scheme 1)	Fused silica capillary coated with γ-Al_2O_3 (d_c = 518 μm, L = 17–50 cm)	Pd/γ-Al_2O_3 (0.003-5.7 wt% Pd)	- Fill the microreactor with a solution of palladium acetate in toluene	Liquid: 3-methyl-1-pentyn-3-ol (0.032-0.3 M) in ethanol Gas: H_2 Ca. 25 °C, 1.1 bar Flow pattern: slug flow	78% yield of 3-methyl-1-penten-3-ol within 1 min residence time	[32]
2	Hydrogenation of 3-methyl-1-pentyn-3-ol (Scheme 1)	Borosilicate glass chip (d_c = 260, 420 μm, L = 1 m)	Pd/silicalite (2 wt% Pd)	- Pretreatment with NH_4F solution - Hydrothermal synthesis with silicalite precursor suspension - Circulate $PdCl_2$ in acetonitrile	Liquid: 3-methyl-1-pentyn-3-ol (0.53 M) in ethanol Gas: H_2 25 °C, 1.5 bar	Ca. 60–80% yield of 3-methyl-1-penten-3-ol; catalyst deactivation over 30 h, possibly by leaching	[33]
3	Hydrogenation of 2-methyl-3-butyn-2-ol (Scheme 2)	Fused silica capillary (d_c = 250 μm, L = 10 m)	Pd/TiO_2 and Pd-Zn/TiO_2 (1 wt% total loading, Pd:Zn = 1:3)	- Coat the microreactor with the solution obtained by mixing Pd or Pd-Zn nanoparticle dispersion, Ti precursors and surfactants in ethanol	Liquid: 2-methyl-3-butyn-2-ol (0.011-0.45 M) in methanol Gas: H_2-N_2 mixture 55–64 °C, ambient pressure Flow pattern: annular flow	90% selectivity to alkene product at 99.9% alkyne conversion over Pd-Zn/TiO_2 catalyst; catalyst stable in 1 month's use	[38]
4	Hydrogenation of 2-methyl-3-butyn-2-ol (Scheme 2)	Fused silica capillary (d_c = 530 μm, L = 2.5–10 m)	Pd-Bi/TiO_2 (2.5-3.3 wt% Pd)	- Pretreatment with NaOH solution - Fill the microreactor with the sol obtained by mixing TiO_2 sol and Pd-Bi nanoparticle dispersion in methanol	Liquid: neat 2-methyl-3-butyn-2-ol or in hexane (1.2 M) Gas: H_2-N_2 mixture 30–70 °C, ambient pressure Flow pattern: slug, slug-annular and annular flows	90% alkene product yield with 50 g/day reactor throughput; no catalyst deactivation for 100 h on stream	[39,40]
5	Hydrogenation of citral (Scheme 3)	Fused silica capillary (d_c = 250 μm, L = 10 m)	Au/TiO_2 (1 wt% Au) and Pt-Sn/TiO_2 (0.95 wt% Pt, 0.51 wt% Sn)	- Pretreatment with NaOH solution - For Au/TiO_2: coat the reactor wall with Au/TiO_2 sol - For Pt-Sn/TiO_2: first coat with TiO_2 sol, then flush with ethanol solution of Pt-Sn metal cluster	Liquid: citral (0.25–10 mM) in 2-propanol Gas: H_2-N_2 mixture 40–80 °C, ambient pressure Flow pattern: annular flow	79% yield of unsaturated alcohols over Pt-Sn/TiO_2 coating within a liquid residence time of 30 min	[41]
6	Hydrogenation of phenylacetylene (Scheme 4)	Fused silica capillary (d_c = 250 μm, L = 9 m)	Pd/TiO_2 (1 wt% Pd)	- Coat with the solution obtained by mixing Pd nanoparticle dispersion, Ti precursors and surfactants in ethanol	Liquid: phenylacetylene (10 vol%) in methano$_l$ Gas: H_2 30–50 °C, ambient pressure Flow pattern: annular flow	Ca. 85% selectivity to styrene at 95% phenylacetylene conversion; catalyst stable in over 1 month's use	[42]
7	Hydrogenation of nitrobenzene (Scheme 5)	Borosilicate capillary (d_c = 200 μm, L = 0.3 m)	Pt/TiO_2	- Fill the microreactor with TiO_2 precursor solution - Fill the microreactor with Pt nanoparticle solution	Liquid: nitrobenzene (50 mM) in 2-propanol; Gas: H_2 40 °C, ambient pressure Flow pattern: slug flow	93% aniline yield at 12 s residence time; catalyst stable during at least 14-h operation	[43]
8	Hydrogenation of nitrobenzene (Scheme 5)	Polytetrafluoroethylene capillary (d_c = 600 μm, L = 1 m)	Pd/polydopamine	- Flush the microreactor with aqueous dopamine solution - Flush with aqueous K_2PdCl_4 solution	Liquid: nitrobenzene (30–90 mM) in ethanol-water mixture Gas: H_2	Over 90% aniline yield at over 97% nitrobenzene conversion during 40-h continuous operation	[44]

(*continued on next page*)

Table 1 (*continued*)

Entry	Reaction	Microreactor[a]	Catalytic coating	Main coating procedure	Operational conditions	Results	Reference
9	Hydrogenation of 2,4-diphenyl-4-methyl-1-pentene (Scheme 6)	Glass capillary (d_c = 530 μm, L = 0.5 m)	Pd/polysilane-TiO_2	- Pretreatment with NaOH solution	Ambient temperature and pressure Flow pattern: slug flow Liquid: 2,4-diphenyl-4-methyl-1-pentene (0.1 M) in tetrahydrofuran; Gas: H_2	Conversion and yield close to 100% within 1 min residence time; 100-h operation without significant loss of activity.	[45]
				- Fill the microreactor with a tetrahydrofuran solution of palladium acetate, TiO_2 and polysilane	Ambient temperature and pressure		
10	Hydrogenation of various substrates (e.g., alkenes and alkynes)	Glass chip (W = 200 μm, H = 100 μm, L = 0.45 m)	Microencapsulated Pd catalyst within a copolymer	- Introduce amine groups onto the microreactor wall	Liquid: substrate in solvent (typically tetrahydrofuran)	Quantitative product yield obtained especially under annular flow (much higher than that obtained in batch reactors)	[46]
				- Pass through the microreactor a colloidal solution made from $Pd(PPh_3)_4$ and a copolymer in dichloromethane-t-amyl alcohol	Gas: H_2		
					Ambient temperature and pressure Flow pattern: slug and annular flows		
11	Aerobic oxidation of alcohols to ketones or aldehydes (Scheme 7; example)	Polysiloxane-coated fused silica capillary (d_c = 250 μm, L = 0.5 m)	Microencapsulated Au and Pd-Au within a copolymer	- Reduce cyano group on the microreactor surface to an amine	Liquid 1: benzylic, aliphatic, allylic, and other alcohols in 1,2-dichloroethane	Excellent aldehyde/ketone yields in microreactors (much higher than those in batch reactors under similar residence times); 4 days of operation without loss of activity	[47]
				- Pump through the microreactor a colloidal Pd-Au or Au solution made from palladium acetate and/or $AuClPPh_3$, $NaBH_4$, and copolymer in tetrahydrofuran	Liquid 2: K_2CO_3 in water or water		
					Gas: O_2 50–70 °C, ambient pressure		
12	Direct synthesis of hydrogen peroxide (Scheme 8)	Polymethylmethacrylate microreactor (W = 1 mm, H = 100 μm, L = 1.36 m)	Pd/C (5 wt% Pd)	- Coat the microreactor by running Pd/C catalyst slurry through	Liquid: 0.1 M HCl in water	H_2O_2 concentration of 8.3 mM at 93 s residence time	[48]
					Gas: H_2-O_2 mixture 5–20 °C, ambient pressure Flow pattern: slug flow		
13	Direct synthesis of hydrogen peroxide (Scheme 8)	Glass capillary (d_c = 530–2000 μm, L = 0.345 m)	Microencapsulated Pd catalyst within a copolymer (1–4 wt% Pd)	- Pretreatment with NaOH solution, water and ethanol	Liquid: 0.1 M HCl and 0.281 mM KBr in methanol	Continuous production for at least 11 days with H_2O_2 concentration at ca. 1.1 wt%	[49]
				- Fill the microreactor with a polymer solution prepared from polystyrene copolymer and $Pd(PPh_3)_4$ in tetrahydrofuran	Gas: H_2-O_2 mixture		
					Ambient temperature and pressure Flow pattern: slug flow		
14	Direct synthesis of hydrogen peroxide (Scheme 8)	Fused silica capillary (d_c = 320 μm, L = 0.5–1.5 m)	Pd-Au/SiO_2 (5 wt% total loading, Au:Pd = 1:2)	- Pretreament with NaOH and HCl solutions	Liquid: 0.05 M sulfuric acid, 9 ppm NaBr in water	5 wt% H_2O_2 at 80% H_2 conversion; safe operation in the explosive regime	[50]
				- Coat with SiO_2 slurry	Gas: H_2-O_2(-N_2) mixture		

(*continued on next page*)

Table 1 (*continued*)

Entry	Reaction	Microreactor[a]	Catalytic coating	Main coating procedure	Operational conditions	Results	Reference
				- Fill the microreactor with a colloidal Pd-Au solution	30–45 °C, 15–25 bar Flow pattern: slug flow		
15	Epoxidation of propene using H_2O_2 (Scheme 9)	Fused silica capillary pre-coated with a silica layer (d_c = 320 µm, L = 3.5–6 m)	Titanium silicate-1	- In-situ hydrothermal synthesis using titanium silicate-1 precursor suspension	Liquid: 13.3 wt% aqueous H_2O_2 with methanol as solvent Gas: propene 40 °C, 6 bar	Propylene oxide (PO) productivity at 2 $g_{PO}/(g_{catalyst}h)$; stable catalyst with small deactivation in 500-h use	[51]
16	Epoxidation of methyl oleate using H_2O_2 (Scheme 10)	Glass capillary (d_c = 530 µm, L = 0.6 m)	TiO_2	- Fill the microreactor with TiO_2 dispersion in ethanol	Liquid 1: H_2O_2, formic acid and stabilizer Liquid 2: methyl oleate 40–70 °C, ambient pressure	43.1% epoxide yield at 2.7 min residence time; coating partially peeled off after 3-h operation	[52]

[a] d_c, W, H and L appeared in the column represent microchannel (hydraulic) diameter, width, height and length, respectively.

as mill-reactors if a strict distinction has to be made according to the channel dimension. This distinction is in effect not very necessary provided that the miniaturization benefits (e.g., transport intensification) at the selected channel dimension well suit the needs of reaction. However, it must be admitted that some physical transport phenomena beneficial for chemical synthesis usually take place below a certain channel diameter (e.g., regular laminar flow, surface-tension dominated droplet/bubble flow, inhibition of explosion propagation for enhanced safety) [29–31], which might justify the preferred deployment of microreactors over mill-reactors for case-specific applications. Therefore, the current review mainly deals with microreactors with internal channel dimensions below ca. 1 mm.

2. Microreactors for heterogeneously catalyzed multiphase reactions

In this section, different microreactor designs suitable for performing heterogeneously catalyzed reactions between (typically gas-liquid or liquid-liquid) immiscible phases are described, including their basic operation principles and selected reaction examples in sustainable chemical synthesis. In brief, solid catalysts can be incorporated into (capillary- or chip-based) microreactors via two main ways: in the form of catalytic wall coatings (the design is specified as wall-coated microreactor; Fig. 1a–b), or as powder particles (the design is specified as packed-bed microreactor; Fig. 1c–d) in an otherwise empty microreactor in which multiphase flow and reaction take place.

2.1. Wall-coated microreactors

A usually way to incorporate solid catalysts into microreactors is by applying a very thin layer of catalytic coatings onto the microreactor inner wall. The relevant research activities started from 1990s with a focus mainly on heterogeneously catalyzed gas-phase reactions, later with an increasing attention paid to multiphase reactions [20,21,36,37].

2.1.1. Immobilization of coatings into microreactors

Table 1 provides an overview of selected reaction examples dealing with the use of catalytic coatings (including the method of immobilization) into capillary- or chip-based microreactors for heterogeneously catalyzed multiphase reactions (the majority being gas-liquid-solid systems). As seen in this table, the immobilization of catalytic wall coatings often involves:

Step 1: pretreatment of the microreactor wall surface. This step serves to increase the adherence of the catalytic layer to the wall [36], typically characterized by chemical pre-treatment, e.g., to increase surface roughness (on substrates like fused silica or glass) using alkali or acid solutions [33,39–41,49,50].

Step 2: application of a porous coating of the catalyst support. This step is to ensure a sufficient geometric surface for performing catalytic reactions and is characterized by depositing a layer of catalyst supports (e.g., SiO_2, γ-Al_2O_3 and TiO_2) onto the (pre-treated) microreactor wall [32,33,41,43,44,50–52], typically using the sol-gel technique (based on the use of a precursor solution or a colloidal dispersion of the material to deposit) or suspension technique (based on the use of a slurry of the finished material to deposit) [36].

Step 3: Immobilization of the catalyst itself (usually noble metal like Pt, Pd or Au) onto the catalyst support, typically using the sol-gel or suspension technique [32,33,41,43,44,50].

In the case of directly using the porous coating prepared in Step 2 as catalyst (e.g., TiO_2 or titanium silicate-1 [51,52]), Step 3 is not involved. Moreover, Steps 2 and 3 can be sometimes combined to deposit the catalyst support and the catalyst itself altogether in one step in the microreactor using the suspension technique [38–40,42,45,48].

Table 1 highlights another immobilization method, characterized by the encapsulation of the colloidal solution of the active catalysts (e.g.,

Pd and Au) into copolymer micelles which are then crosslinked with functional groups (e.g., the introduced amine groups) on the (pre-coated) microreactor wall surface via a chemical modification step [46,47,49].

The uniform deposition of a catalytic layer around microreactor walls (with thickness usually on the order of 1–10 μm) has been attempted in the literature using the static coating method (typically characterized by completely filling the microreactor channel with a sol-gel solution or slurry, sealing one end and evaporating solvent on the other end), and dynamic coating method such as the gas displacement method (characterized by a flow of gas leaving a thin liquid/slurry layer along the wall) [39]. A direct hydrothermal synthesis was applied in the case of immobilizing zeolite layer onto microreactor walls [33,51], which can lead to better coating uniformity and adherence when compared with the above-mentioned coating methods [36]. More details about the general coating methods on various microreactor substrates for use in different types of reaction cases can be found in the recent literature [20,21,36,37].

2.1.2. Transport characteristics

Multiphase flow pattern in wall-coated microreactors resembles those found in an empty microchannel. For heterogeneously catalyzed gas-liquid reactions as mainly covered in Table 1, two frequently encountered flow patterns are gas-liquid slug flow (characterized by an alternate passage of elongated bubbles and liquid slugs through the microchannel coated with solid catalysts; Fig. 2a), and annular flow (characterized by a continuous flow of gas in the core surrounded by a continuous flow of liquid film around the wall coating; Fig. 2b) [53]. For a given superficial liquid velocity (e.g., far below 1 m/s), gas-liquid slug flow dominates at relatively low gas-liquid flow ratios and annular flow takes over at very high gas-liquid flow ratios, where a transitional slug-annular flow exists at intermediate gas-liquid flow ratios and resembles an annular flow except the presence of periodical interruption of the flow by large-amplitude waves [53,54]. In slug flow (Fig. 2a), a thin liquid film is usually present between the gas bubble and catalytic coating if the coating is well wetted by liquid, which otherwise requires a fine tuning of the coating wettability in order to ensure a good reactant-catalyst contact [55]. Operational ranges of the above flow patterns can be predicted from those empirical flow transition correlations that have been proposed for use in microreactors, based on either superficial velocities or more generic dimensionless numbers for operation under ambient conditions as well as elevated pressure conditions [56,57].

The confinement of gas-liquid flow in microreactors has created a very high gas-liquid interfacial area (e.g., on the order of 10,000 m^2/m^3) [54]. This, combined with superior flow and mass transfer property of slug flow (e.g., in the reduced axial mixing and enhanced radial mixing, narrowed residence time distribution) or annular flow (e.g., in the fast diffusion within the thin liquid film and large availability of gaseous reactant), ensures significantly intensified gas-liquid mass transfer rates beneficial for an improved reaction performance [19]. Typically, the overall volumetric liquid-phase mass transfer coefficient in microreactors increases from slug flow all the way to annular flow at a given superficial liquid velocity and has been reported on the order of 1–10 s^{-1} that is at least one or two orders of magnitude higher than those in conventional gas-liquid reactors [54]. When it comes to wall-coated microreactors, the incorporation of a thin layer of catalytic coating (with thickness usually on the order of 1–10 μm) into an otherwise empty microchannel not only ensures a low pressure drop (e.g., if the reactor/coating length is not extremely long) and fast heat transfer within the catalyst layer to avoid the formation of hot spots (e.g., in the presence of a strongly exothermic reaction), but also largely eliminates the internal diffusion resistance associated with liquid reactants transporting in the catalyst layer, thereby allowing the intrinsic kinetic rates more easily approached compared with conventional reactors [58]. A quantitative description of the wall-coated microreactor performance herein requires the development of microreactor models accounting for the external gas-liquid-solid transport, internal diffusion in the catalyst layer and its coupling with chemical kinetics, which has been greatly facilitated by the presence of approximate correlations for describing gas-liquid/liquid-solid mass transfer and the coating effectiveness factor [19,54,59–64].

Liquid-liquid-solid reactions have been rarely dealt with in continuous flow reactors [65], but are expected to have promising applications in heterogeneously catalyzed aqueous-organic synthesis (to be discussed later). One such example is included in Table 1 regarding the use of wall-coated microreactors for epoxidation of methyl oleate [52], however, no liquid-liquid flow pattern information was given. In general, one favorable liquid-liquid flow pattern for the operation of wall-coated microreactors is slug flow in which droplets travel through the microchannel and are separated by slugs of a continuous liquid carrier (Fig. 2a). This flow pattern exists at a relatively low flow ratio of the dispersed liquid phase to the continuous liquid phase [66], and its operational range can be predicted using those empirical criteria available in the literature [67–69]. (Semi-)empirical liquid-liquid slug flow mass transfer correlations were also proposed [19,70–72]. Given similarities between gas-liquid and liquid-liquid slug flows in terms of transport properties, models developed for wall-coated microreactors in the former case can be usually modified for use in the latter case as well.

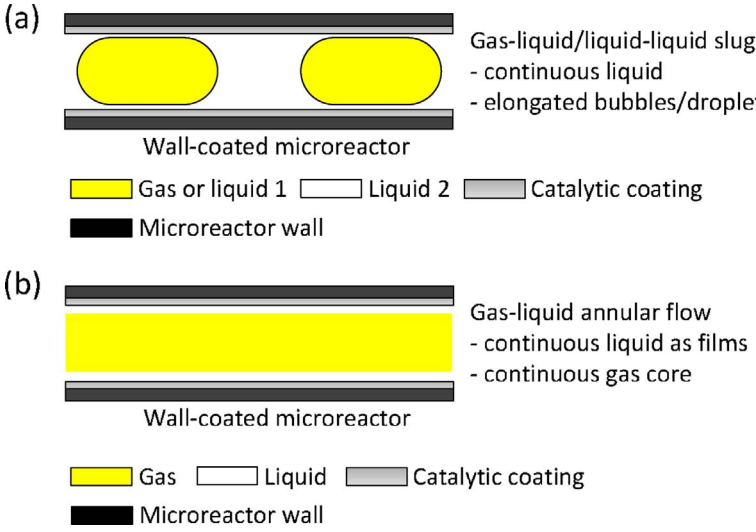
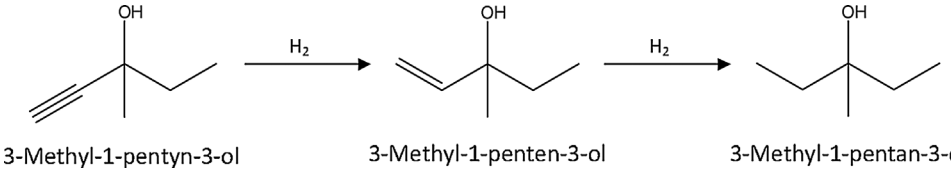


Fig. 2. Representative gas-liquid and liquid-liquid flow patterns in wall-coated microreactors. (a) Gas-liquid or liquid-liquid slug flow (a perfect wetting of the catalytic wall coating by the continuous liquid phase is assumed). (b) Gas-liquid annular flow (the liquid film can be wavy or smooth depending on the flow conditions).



Scheme 1. Selective hydrogenation of 3-methyl-1-pentyn-3-ol to the desired 3-methyl-1-penten-3-ol, and the overhydrogenation to 3-methyl-1-pentan-3-ol.

2.1.3. Selected reaction examples

Wall-coated microreactors have been explored in promising chemical syntheses in the presence of immiscible phases such as selective gas-liquid hydrogenation, aerobic oxidation of alcohols, direct combination of hydrogen and oxygen for hydrogen peroxide synthesis, epoxidation with aqueous H_2O_2 solutions (Table 1). For these reactions, the overall reaction rate in conventional reactors is often limited by interphase mass transfer especially when the reaction kinetics is fast. By performing such multiphase reactions over a thin catalyst layer coated in microreactors, mass transfer rate is substantially enhanced. This, plus unique reaction parameter control in microreactors, can lead to a much improved reaction performance.

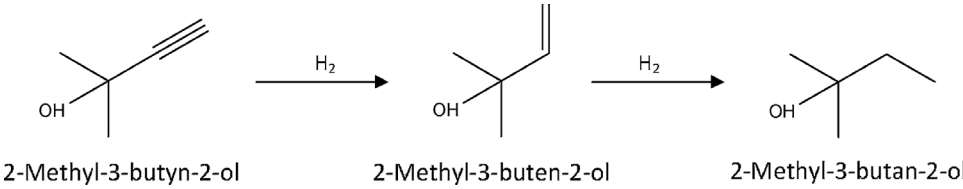
2.1.3.1. Selective hydrogenation. Selective hydrogenation (e.g., of functionalized alkynes to alkenes, of unsaturated aldehydes to unsaturated alcohols) represents an important step towards the synthesis of pharmaceuticals, fine chemicals, flavours and fragrances [73,74].

Hydrogenation of 3-methyl-1-pentyn-3-ol to the desired 3-methyl-1-penten-3-ol as a model reaction (Scheme 1; Table 1, entry 1) has been performed under gas-liquid slug flow in a fused silica capillary microreactor coated with 0.003-5.7 wt% Pd/γ-Al_2O_3 catalysts (Fig. 1a) under near ambient conditions [32]. It is shown that a fast mass transfer rate in the microreactor could eliminate transport limitation and thus allowed the reaction to run under intrinsic kinetic control. A significantly reduced axial dispersion in slug flow enabled a precise control of the residence time required for the target yield: a yield of 3-methyl-1-penten-3-ol at about 78% could be achieved within 1 min residence time and the overhydrogenation to 3-methyl-1-pentan-3-ol was largely suppressed. The catalytic coating exhibited no deactivation during several weeks' use. Furthermore, an additional advantage in the current operation is that the reaction conversion could be monitored by a visual inspection of the shrinking H_2 bubbles in flow, providing a hands-on control over the catalyst activity and a fast process optimization. The same model reaction has been tested in borosilicate glass microreactor chips coated with 2 wt% Pd/silicalite (Fig. 1b; Table 1, entry 2) [33]. While a maximum yield of 3-methyl-1-penten-3-ol at around 60–80% could be obtained due to an improved residence time and/or mass transfer control in the microreactor as compared with results in a conventional batch autoclave, a catalyst deactivation was noticed over 30 h on stream and was possibly caused partially by palladium leaching. Thus, the palladium attachment to the silicalite support in the catalyst coating still needs to be improved, where one possible strategy to be explored is to functionalize the catalyst support with amine groups that bind strongly to Pd nanoparticles.

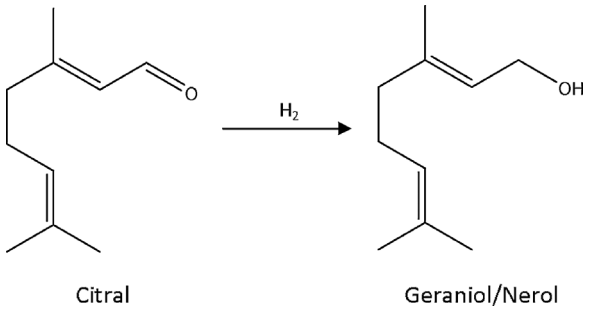
A similar reaction, selective hydrogenation of 2-methyl-3-butyn-2-ol to 2-methyl-3-buten-2-ol (Scheme 2), has been tested in fused silica capillary microreactors, where titania-supported monometallic (Pd) or bimetallic (Pd-Zn, Pd-Bi) catalysts with Pd loading up to 3.3 wt% were immobilized as wall catalytic coatings [38–40]. The reaction was operated under slug, slug-annular and annular flows in these microreactors up to 70 °C and under near ambient pressure conditions (Table 1, entries 3–4). It appeared that the addition of Zn or Bi in the coating considerably improved the alkene selectivity due to the poisoning of sites of Pd nanoparticles that were most active for overhydrogenation. As an example, 90% alkene selectivity was obtained at 99.9% alkyne conversion in the microreactor with Pd-Zn/TiO_2 catalyst using methanol as solvent, in comparison with a maximum 81.1% selectivity at 96% conversion obtained in a batch autoclave employing the same catalyst spin-coated on silicon substrates and a higher H_2 pressure [38]. No catalyst deactivation was noticed during a continuous 1-month operation, suggesting that metal leaching was negligible due to a strong metal-support interaction in the prepared catalyst coatings. Over Pd-Bi/TiO_2 catalyst, it was further shown that solvent-free hydrogenation could be performed in the microreactor with a highest alkene yield of 90% (corresponding to a microreactor production capacity of 50 g per day) [40]. However, Bi leaching from Pd catalysts was found under solvent-free conditions (mainly caused by oxidation of metallic Bi species), but can be fully suppressed in the presence of 1 vol % acetic acid in the reaction mixture. With the latter improvement, the catalyst remained stable over 100 h on stream. The obtained results here revealed the feasibility of capillary-based microreactors for fine chemicals synthesis on a small scale. It is envisaged that the product throughput in microreactors can be increased to more industrially relevant scale (e.g., to an order of 10–100 kg per day) by combining additional process intensification (e.g., operation under much higher hydrogen pressures) and the external numbering up of a single capillary to multiple capillary microreactor assemblies running in parallel [38–40].

The use of microreactors for an efficient synthesis as well as a reliable kinetic study has been demonstrated with another model reaction, hydrogenation of citral (3,7-dimethyl-2,6-octadienal) (Scheme 3; Table 1, entry 5) [41]. The interior walls of fused silica capillary microreactors were supported with Au/TiO_2 and Pt-Sn/TiO_2 catalysts. Annular flow operation was chosen to improve gas-liquid mass transfer in order to obtain kinetic data. The prepared Pt-Sn/TiO_2 catalyst showed a higher yield (maximum of 79% at a liquid residence time of 30 min and temperature of 70 °C using pure hydrogen) towards unsaturated alcohols (mainly geraniol and nerol) than Au/TiO_2 under the same reaction conditions. The positive effect of Sn addition on the catalyst performance was well explained by the developed reaction kinetics in microreactors: as compared to Au/TiO_2, the adsorption of unsaturated alcohols onto Pt-Sn/TiO_2 was prevented until almost a full citral conversion; hydrogenation of citral on Pt-Sn/TiO_2 was more preferred over the subsequent hydrogenation of unsaturated alcohols.

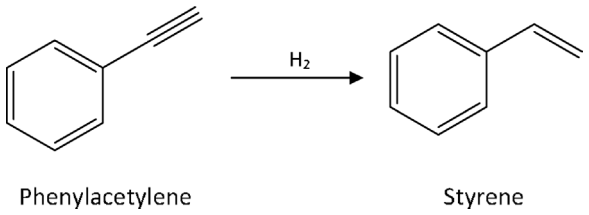
The incorporation of stable Pd nanoparticles into the mesoporous TiO_2 thin film as wall coatings of a fused silica capillary microreactor has been used for carrying out selective hydrogenation of phenylacetylene to styrene under gas-liquid annular flow pattern (Scheme 4; Table 1, entry 6) [42]. This reaction is industrially important as



Scheme 2. Selective hydrogenation of 2-methyl-3-butyn-2-ol to the desired 2-methyl-3-buten-2-ol, and the overhydrogenation to 2-methyl-3-butan-2-ol.



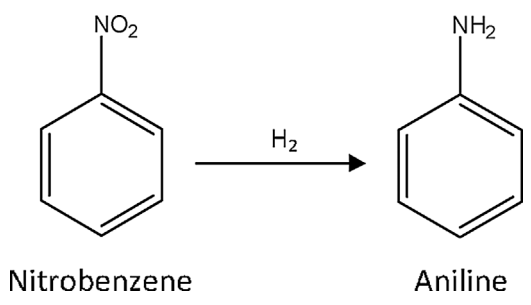
Scheme 3. Hydrogenation of citral towards unsaturated alcohols.



Scheme 4. Hydrogenation of phenylacetylene to styrene.

phenylacetylene present in styrene feedstocks has to be lowered to below ca. 10 ppm, otherwise it will lead to deactivation of the styrene polymerization catalyst [75]. Over 1 wt% Pd/TiO_2 catalyst, the selectivity towards styrene as the intermediate hydrogenation product in the microreactor increased with decreasing liquid flow rate, whereas the conversion of phenylacetylene was reduced. Therefore, a phenylacetylene conversion close to 95% with over 85% yield towards styrene could be achieved by carefully controlling the residence time, gas-liquid flow ratio and temperature. The coated catalyst was found very active, given the turnover frequency (TOF) comparable to that reported for the case using a colloid solution of Pd nanoparticles as homogeneous catalyst. Moreover, the prepared capillary microreactor remained active and selective for a period of 1000 h time-on-stream, showing good prospects for long-term operation.

Aniline as an important chemical in the plastics industry can be produced via catalytic hydrogenation of nitrobenzene [76]. Most industrial processes are performed in the gas phase in conventional large packed-bed reactors while the liquid-phase hydrogenation is not deployed extensively mainly due to the difficulties in the reaction heat removal [77]. Wall-coated microreactors have thus promising uses in such liquid-phase hydrogenation of nitrobenzene (Scheme 5), given their high surface area/volume ratio beneficial for enhanced heat/mass transfer rates which largely enable reaction under isothermal conditions and kinetically controlled regime for obtaining a favorable target product yield. Capillary microreactors made of borosilicate glass and polytetrafluoroethylene (PTFE) with coatings of TiO_2- and polydopamine layer-supported Pd catalysts, respectively, have shown great effectiveness in this hydrogenation reaction (Table 1, entries 7–8), which could provide an aniline yield of over 90% under gas-liquid slug



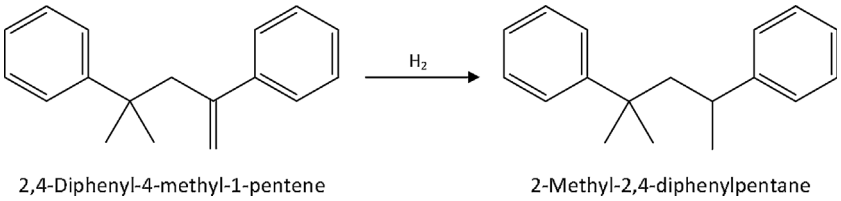
Scheme 5. Hydrogenation of nitrobenzene to aniline.

flow operation at very short residence times (e.g., 12 s in the former case) [43,44]. A stable catalytic activity of Pd/TiO_2 coating was maintained over at least 14 h' operation if the residence time was long enough to ensure an almost complete nitrobenzene conversion, so that there was insufficient intermediate product (nitrosobenzene) adsorbed on the catalyst which otherwise could cause catalyst deactivation [43]. The corresponding microreactor system could afford a TOF value 5.5 times that obtained in a batch reactor using the same type of catalyst under similar conditions. For the microreactor with polydopamine layer-supported Pd catalyst as wall coatings, no deactivation was noticed during a 40-h continuous operation [44].

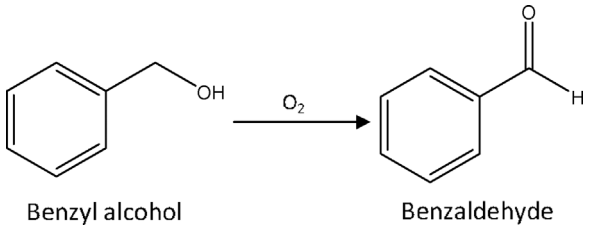
Pd catalysts microencapsulated within the backbone of a copolymer that was crosslinked with functional groups on the glass microreactor wall were also reported for achieving a good catalyst adhesion and an efficient catalysis in hydrogenation reactions [45,46]. For example, polysilane-TiO_2 supported Pd catalysts immobilized onto the inner surface of glass capillary microreactors were shown to catalyze hydrogenation of various substrates (e.g., alkenes and alkynes, nitrobenzene) efficiently. Typically, when using 2,4-diphenyl-4-methyl-1-pentene as a model substrate, a close to 100% yield of the target product 2-methyl-2,4-diphenylpentane (Scheme 6; Table 1, entry 9) could be achieved within 1 min residence time [45]. The microreactor could be used for at least 100-h continuous flow hydrogenation without any activity decrease if an optimized temperature of crosslinking was selected during the catalyst preparation. Moreover, Pd catalyst microencapsulated within one copolymer was immobilized in a glass microreactor chip and has shown great efficiency in catalyzing hydrogenation reactions (e.g., reduction of double bonds including tri-substituted olefins, and triple bonds; deprotection of a benzyl ether and of a carbamate group) (Table 1, entry 10) [46]. Quantitative product yields were obtained under annular flow operation within a mean residence time of 2 min, which were much higher than those obtained in batch reactors. In contrast, slug flow operation in the microreactor rendered insufficient product yields, possibly due to comparatively low mass transfer rate therein. No Pd leaching was detected in most cases and no loss of activity was noticed during a reuse of the developed microreactors for several times.

2.1.3.2. Selective aerobic oxidation of alcohols. The oxidation of primary and secondary alcohols into the corresponding carbonyl compounds is one important and essential transformation in organic synthesis [78]. Heterogeneous catalysis, in combination with the use of molecular oxygen as the clean oxidant, represents a greener approach than the tradition one employing stoichiometric quantities of inorganic oxidants. Such multiphase reactions often suffer from limited interphase mass transfer, rendering an insufficient reaction performance. Excellent mass transfer capabilities in wall-coated microreactors can thus provide an attractive solution.

Au and Pd-Au nanoparticles microencapsulated within a copolymer have been immobilized in polysiloxane-coated capillary microreactors (Table 1, entry 11) and thus developed microreactor systems have been tested in the aerobic oxidation of benzylic, aliphatic, allylic and other alcohols (dissolved in 1,2-dicholorethane) in the presence of water or an aqueous K_2CO_3 solution [47]. The reaction proceeded smoothly in the microreactor to produce the corresponding aldehydes and ketones in good to excellent yields. For instance, 1-phenylethanol was oxidized into the corresponding ketone (yield > 96%) over the coated Au catalyst within a mean residence time of 90 s. In comparison, performing this reaction in a batch reactor using the same catalyst only gave 1% yield at the same residence time, which highlighted the critical importance of an access to high interfacial mass transfer rate. For the selective oxidation of benzyl alcohol as a model substrate in such Au-immobilized microreactors (Scheme 7), the yield of the target product benzaldehyde was only 53% at an alcohol conversion of > 99%. However, using the microreactor coated with bimetallic Au-Pd catalyst, the yield of benzaldehyde could be increased to 92%. Regarding the



Scheme 6. Hydrogenation of 2,4-diphenyl-4-methyl-1-pentene to the target product 2-methyl-2,4-diphenylpentane.

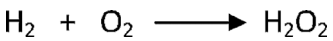


Scheme 7. Oxidation of benzyl alcohol to benzaldehyde.

catalyst stability, no gold leaching was noticed and the microreactor systems could be used continuously without activity loss for at least 4 days.

2.1.3.3. Direct synthesis of hydrogen peroxide. Hydrogen peroxide, an important commodity chemical, is currently used as bleach in the pulp and paper industry, disinfectant in the cosmetics and pharmaceutical industry, and environmentally friendly oxidant for the synthesis of fine chemicals. The direct combination of H_2 and O_2 to produce H_2O_2 (e.g. in the aqueous solution over Pd-based catalysts; Scheme 8) is considered as a greener alternative to the current industrial route based on the complex and less atom efficient anthraquinone autoxidation process [79]. The direct synthesis of H_2O_2 in conventional gas-liquid-solid reactors is a challenging task given the explosion risks of H_2-O_2 gas mixtures over a wide range (5–95 vol%), the presence of mass transfer resistance due to the tri-phasic nature of the process, and the control of selectivity towards H_2O_2. To avoid the explosion risks, usually highly diluted gas feed mixtures are used and thus the reaction needs to be operated under high pressure in order to improve mass transfer from gas to liquid. In this respect, (wall-coated) microreactors offer an attractive processing option. Microreactors can be considered intrinsically safe (especially if the internal channel dimension is sufficiently small), because of a very large surface-to-volume ratio ensuring an effective quenching of free radicals and efficient removal of the reaction heat [80]. Thus, the direct synthesis of H_2O_2 can be safely handled in microreactors using the concentrated H_2-O_2 mixtures, reducing the need for high pressure operation. This, combined with the inherently high mass transfer rates therein and the deposition of active catalytic coatings (i.e., increasing the catalyst utilization efficiency), can to a large extent ensure an efficient H_2O_2 production.

A preliminary research in this direction has been shown in the use of a stacked polymethylmethacrylate (PMMA) plate-type microreactor coated with 5 wt% Pd/C catalyst for the direct synthesis of H_2O_2 (Table 1, entry 12), where H_2 and O_2 were produced by water electrolysis [48]. When using a 0.1 M HCl solution as the liquid phase, a H_2O_2 concentration of 8.3 mM (< 0.1 wt%) could be achieved in the microreactor under slug flow operation at a residence time of 93 s, reaction temperature of 10 °C and ambient pressure conditions. In contrast, a much lower H_2O_2 concentration of 3.4 mM was obtained in a batch slurry reactor after 3 h reaction time under similar conditions, showing the great mass transfer intensification potential of wall-coated microreactors.

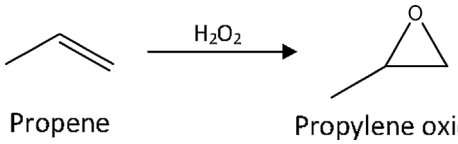


Scheme 8. Direct combination of H_2 and O_2 to form H_2O_2.

Later, by coating onto the inner wall of glass capillary microreactors with a thin film of a copolymer based on a polystyrene backbone with microencapsulated Pd (loading: 1–4 wt%), a much higher H_2O_2 concentration at around 1.1 wt% could be obtained in such developed microreactor systems from a direct combination of H_2 and O_2 in the explosive regime, using a solution of 0.1 M HCl and 0.281 mM KBr in methanol at ambient temperature and pressure (Table 1, entry 13) [49]. Here, methanol instead of water was used as solvent to improve mass transfer due to a higher solubility of H_2 and O_2 therein, while the addition of HCl and KBr effectively suppressed the unwanted H_2O_2 hydrogenation and decomposition. The long-term catalyst stability has been demonstrated during an 11-day continuous operation under slug flow, despite a slight activity drop between days 4–6 (which was possibly contributed by palladium leaching and nanoparticle size growth). Moreover, a decreased H_2O_2 concentration at the outlet was found with decreasing capillary diameters under otherwise the same conditions, due to the significantly smaller catalyst amount deposited on the wall of narrower capillaries. Thus, an optimization of the processing conditions (e.g., flow rates) would be necessary in the latter case.

A further increase of H_2O_2 product concentration to 5 wt% from the direct combination of H_2 and O_2 under the explosive regime has been recently demonstrated in a fused silica capillary microreactor, in the presence of SiO_2-supported bimetallic Pd-Au catalyst as immobilized wall coatings (total metal loading: 5 wt%; Table 1, entry 14) [50]. This significantly higher concentration was realized at around 80% H_2 conversion, using an aqueous solution of 0.05 M H_2SO_4 and 9 ppm NaBr as the liquid phase, under mild temperatures (30–45 °C) and high pressures (20–25 bar), and large gas-liquid flow ratios (under slug flow operation). An increase of the partial pressures of H_2 and O_2 was found to increase the selectivity towards peroxide as well as its concentration, which could be due to a combination of the improved mass transfer and a high surface coverage of H_2 and O_2 on the catalyst blocking sites responsible for peroxide decomposition. It appeared that the overall reaction rate was still limited by diffusion within the catalyst layer given a fast gas to solid mass transfer present in the microreactor, which necessitates a further research effort in the fine-tuning of catalyst coatings (e.g., thickness) towards maximized reaction rates. Nevertheless, a significant H_2O_2 selectivity loss was present with the generation of high peroxide concentrations, due to the subsequent H_2O_2 hydrogenation and decomposition. To address this challenge, other process options might be considered, e.g., to operate the microreactor at low H_2O_2 concentration output in order to keep a high selectivity and then to concentrate the solution via distillation, or to couple the direct H_2O_2 synthesis with consecutive reaction for an in-situ peroxide consumption in one microreactor system.

2.1.3.4. Organic synthesis using hydrogen peroxide. Hydrogen peroxide as a green oxidant next to molecular oxygen has many important uses in organic synthesis. Typically, it has shown promising uses in heterogeneously catalyzed reactions for obtaining a favorable product yield, e.g., in the oxidation of alcohols to carbonyl compounds, and epoxidation of simple olefins or functionalized olefins containing an ester, ether or α,β-enone linkage to the corresponding epoxides (important intermediates for the synthesis of various polymers and fine chemicals) [81,82]. Such cases often involve the presence of a tri-phasic (gas-liquid-solid or aqueous-organic-solid) system. Thus, the creation of high interfacial areas and elimination of mass transfer



Scheme 9. Epoxidation of propene to propylene oxide using H_2O_2.

resistances are favorable for an optimized synthesis performance, where microreactors represent an attractive alternative to conventional reactors like batch slurry reactors.

The epoxidation of propene to propylene oxide using H_2O_2 (in water-ethanol mixture) has been demonstrated over titanium silicate-1 (TS-1) catalysts that were in-situ synthesized under hydrothermal conditions on the inner walls of fused silica capillary microreactors (Scheme 9; Table 1, entry 15) [51]. Under gas-liquid processing in the microreactor at a reaction temperature of 40 °C and propene pressure of 6 bar, a propylene oxide (PO) productivity larger than 2 $g_{PO}/(g_{catalyst}.h)$ could be achieved with a PO selectivity above 90% and is still higher than the industrially relevant target at 1 $g_{PO}/(g_{catalyst}.h)$. However, Ti loading in the TS-1 coating still needed to be increased (e.g., by increasing the initial silica precoating thickness) in order to obtain a higher PO productivity comparable to what was reported over bulk synthesized catalysts in conventional reactors. During a 500-h continuous operation, the coating only showed a small deactivation possibly due to coking and the activity could be recovered in a regeneration step using aqueous H_2O_2 solution. This implies the enhanced stability of thus prepared TS-1 coating and a limited Ti leaching, which could be attributed to the minimized number of defective sites formed during the nucleation and growth of TS-1 coating in the microreactor.

Epoxide of methyl oleate (i.e., methyl epoxystearate) finds important applications in the manufacture of lubricants, plasticizers in polymers, cosmetics and pharmaceuticals, and is also a promising biofuel additive [83]. The conventional method for such epoxidation (Prilezhaev reaction) involves the use of mineral acids to catalyze the reaction between hydrogen peroxide and acetic acid/formic acid in order to form a peracid which subsequently epoxidizes the double bond. A switch to heterogeneous catalysis represents a greener approach to simplify the product work-up and catalyst separation/reuse [84,85]. Also performing such synthesis in conventional (semi-)batch reactors features long-hour operation in order to tackle the highly exothermic nature of the reaction and insufficient mixing between aqueous and organic phases. A greener and more efficient route has been investigated by conducting the epoxidation of methyl oleate in glass capillary microreactors coated with TiO_2 catalyst under aqueous-organic continuous flow processing (Scheme 10; Table 1, entry 16) [52]. An epoxide yield of 43.1% was achieved at a temperature of 60 °C and residence time of 2.7 min in the microreactor, using H_2O_2 and formic acid with ethylenediaminetetraacetic acid as stabilizer in the aqueous feed, and neat methyl oleate in the organic feed. The epoxide production rate in microreactors, albeit at such a short residence time, was approximately 23 times that obtained in a batch reactor operated at 15 min. However, after 3-h continuous operation, TiO_2 layer was partially peeled off from the microreactor wall, thus the long-term catalyst adhesion needed to be substantially improved (e.g., by optimizing the coating procedures including solvent evaporation step).

2.1.4. Opportunities and challenges ahead

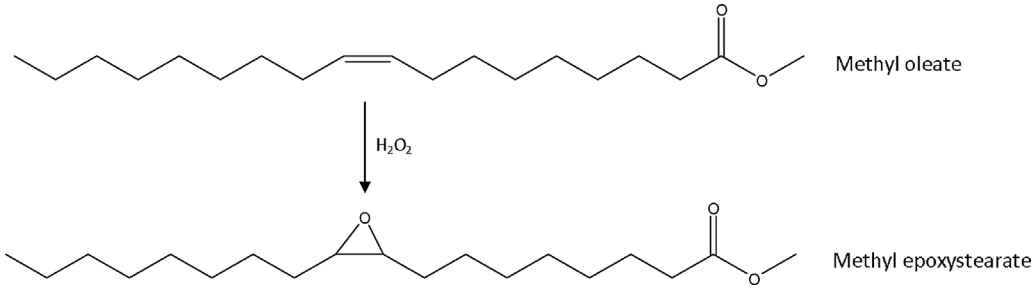
The above reaction examples have showcased the promising application potential of wall-coated microreactors (cf. Table 1). The majority of researches in this field have been focused on gas-liquid-solid hydrogenation and direct H_2O_2 synthesis, and thus more research attention needs to be directed towards other important reaction categories, especially those including heterogeneously catalyzed selective oxidation using either H_2O_2 or O_2 and gas-liquid reactions involving the presence of reactive gases that are not covered in Table 1 (e.g., CO and CO_2) [23]. A low gas pressure close to 1 bar was often used in the existing gas-liquid-solid reaction studies [32,33,38–49], which implies an opportunity for significantly enhanced reaction rates or production capacity by operation under higher pressure conditions. To achieve a long-term stability of catalytic coatings (especially in terms of negligible metal leaching and good catalyst adhesion) relevant to industrial applications remains as a common challenge, although some promising results have been demonstrated [39,40,42,49,51]. In the latter case, an in-depth fundamental understanding into the preparation-structure-activity relationship for the developed catalytic coating is necessary towards obtaining a rational catalyst and process design in microreactors.

2.2. Packed-bed microreactors

Solid catalysts can be directly packed in capillary- or chip-based microreactors in the form of powder particles. This straightforward and convenient way of catalyst incorporation makes it possible to directly use commercially off-the-self catalysts or conventionally synthesized bulk catalysts in the laboratory, and thus greatly expands the application arena of microreactors in solid-catalyzed multiphase reactions. Table 2 provides a brief overview of heterogeneously catalyzed multiphase reactions in packed-bed microreactors, the majority of which involve the presence of a gas-liquid-solid system [34,35,86–93], except only 1 example concerning a liquid-liquid-solid system [94].

2.2.1. Incorporation of powder catalysts into packed-bed microreactors

To fit the microchannel size and especially to avoid unwanted wall flow inside packed-bed microreactors (e.g., the ratio of column diameter to particle diameter should be kept sufficiently large as shown in conventional trickle-bed reactors [95]), the chosen catalysts usually have to be further crushed and sieved to a size well below the microchannel diameter (e.g., on the order of 10–100 μm; Table 2). Thus processed catalysts can be loaded into the microchannel either by manual filling, or by applying a pump or vacuum at the reaction outlet (e.g., when the catalysts are suspended in a liquid). The packed catalysts are retained inside the reaction microchannel by constrictions at both ends, e.g., using micro-pillars in the case of chip-based microreactors [34,86] or filters in the case of capillary-based microreactors [87].



Scheme 10. Epoxidation of methyl oleate to the corresponding epoxide.

Table 2
An overview of multiphase reactions performed in packed-bed microreactors.

Entry	Reaction	Microreactor[a]	Catalyst	Operational conditions	Results	Reference
1	Hydrogenation of 2-methylfuran (Scheme 11)	4-channel silicon-Pyrex chip ($W = H = 400$ μm, $L_{bed} = 47$ mm)	5 wt% Pd/C (Size: 36–53 μm)	Liquid: neat 2-methylfuran; Gas: H_2; 25–160 °C, 45 bar	Ca. 45% conversion of 2-methylfuran at 160 °C with selective production of 2-methyltetrahydrofuran	[86]
2	Hydrogenation of o-nitroanisole (Scheme 12)	Stainless steel capillary ($d_C = 775$ μm; $L_{bed} = 1$–6 cm)	2 wt% Pd/zeolite (Size: 45–75 and 75–150 μm)	Liquid: o-nitroanisole (0.4–6 M) in methanol; Gas: H_2; 25–55 °C, ca. 3–18 bar Flow pattern: slug flow before the reactor	Intrinsic kinetic data obtained in the microreactor	[87,88]
3	Hydrogenation of 2-ethylanthraquinone (Scheme 13)	Stainless steel capillary ($d_C = 775$ μm; $L_{bed} = 7.5$ cm)	1 wt% Pd/SiO_2 (Size: 75–150 μm)	Liquid: 2-ethylanthraquinone (0.22-0.44 M) in a polar/non-polar solvent mixture; Gas: H_2 30–80 °C, 7 bar Flow pattern: slug flow before the reactor	Space time yield in the microreactor 30–50 times that in a conventional packed-bed reactor or batch slurry reactor	[89]
4	Oxidation of benzyl alcohol (Scheme 7)	Silicon-glass chip ($W = 600$ μm, $H = 300$ μm, L_{bed} = typical 3.2 mm)	0.05 wt% Au-0.95 wt% Pd/TiO_2 (Size: ca. 65 μm)	Liquid: benzyl alcohol; Gas: O_2 120 °C, 1 bar Flow pattern: liquid-dominated slug flow and gas-continuous flow	> 90% benzyl alcohol conversion with > 80% benzaldehyde selectivity by operation in gas-continuous flow pattern (fully wetted catalyst)	[34]
5	Oxidation of benzyl alcohol and HMF (Schemes 7 and 14)	Teflon capillary ($d_C = 1.65$ mm, L_{bed} = typical 0.3 m)	Silica-immobilized TEMPO catalyst (Size: 160–240 μm)	Liquid: 5 mol% HNO_3, 0.5 M benzyl alcohol or 0.41 M HMF in 1,2-dichloroethane; Gas: O_2 55 °C, 5 bar Flow pattern: slug flow before the reactor	98% benzyl alcohol conversion with 99% selectivity to benzaldehyde at 0.5 min residence time; no catalyst decomposition over 8 h; 97% HMF conversion with 98% selectivity to DFF at 2 min residence time	[90]
6	Oxidation of cinnamyl alcohol (Scheme 15)	PTFE capillary ($d_C = 800$ μm, $L = 0.3$ m)	1 wt% Au-Pd/TiO_2; (Size: 53–63 μm)	Liquid: cinnamyl alcohol (0.5 M) in toluene; Gas: O_2-N_2 mixture; 80–120 °C, 4 bar Flow pattern: slug flow before the reactor	At 120 °C and using pure oxygen, initial alcohol conversion at 58%, dropped to 33% at 7 h	[91]
7	Oxidation of 4-isopropylbenzaldehyde (Scheme 16)	Silicon-Pyrex chip (27 × 2 × 0.6 mm)	5 wt% Pt/Al_2O_3	Liquid: isopropylbenzaldehyde (1.5 M) in n-butyl acetate; Gas: O_2 90 °C, 2 bar	A yield of cumic acid at 95% achieved at a residence time of seconds	[86]
8	Direct synthesis of hydrogen peroxide (Scheme 8)	10-channel silicon-Pyrex chip ($W = 625$ μm; $H = 350$ μm, $L = 20$ mm)	5 wt% Pd/C (Size: 50–75 μm)	Liquid: 50 mM H_2SO_4, 15 mM H_3PO_4, 0.0051 or 0.51 mM NaBr in water; Gas: H_2/D_2–O_2–N_2 mixture; 20 °C, 20–30 bar Flow pattern: slug flow before the reactor	Selectivity to H_2O_2 close to 100%; 0.2 wt% H_2O_2 solution produced in one microreactor; 0.6 wt% in two microreactors in series	[92]
9	Direct synthesis of hydrogen peroxide (Scheme 8)	Glass chip ($W = 600$ μm; $H = 300$ or 900 μm, $L_{bed} \approx 40$ mm)	5 wt% Pd/Al_2O_3	Liquid: 25 mM H_2SO_4, 5 mM H_3PO_4, 0.51 mM NaBr in water; Gas: O_2–N_2–D_2 mixture; 20 °C, 10–20 bar Flow pattern: slug flow before the reactor	> 3 wt% H_2O_2 solution produced; stable operation for over 1 week	[93]
10	Direct synthesis of hydrogen peroxide (Scheme 8)	Two glass chips ($W = 600$ μm; $H = 900$ μm, $L_{bed} = 40$ and 200 mm)	Pd/TiO_2 and Pd-Au/TiO_2 (1 wt% Pd)	Liquid and gas: the same as entry 9 above; 20 °C, ca. 10 bar at outlet Flow pattern: slug flow before the reactor	Ca. 10 wt% H_2O_2 solution produced over both catalysts	[35]
11	Biodiesel synthesis (Scheme 17)	Aluminum alloy plate-type microreactor ($W = 1$ mm; $H = 500$ μm, $L = 60$ mm)	CaO	Liquid 1: methanol with 2-propanol; Liquid 2: refined palm oil 65 °C, ambient pressure at outlet Flow pattern: slug flow before the reactor	> 98% yield of methyl esters at 6.5 min residence time	[94]

[a] d_c, W, H and L, L_{bed} appeared in the column represent (hydraulic) diameter, width, height, length of microchannel, and length of the catalyst bed, respectively.

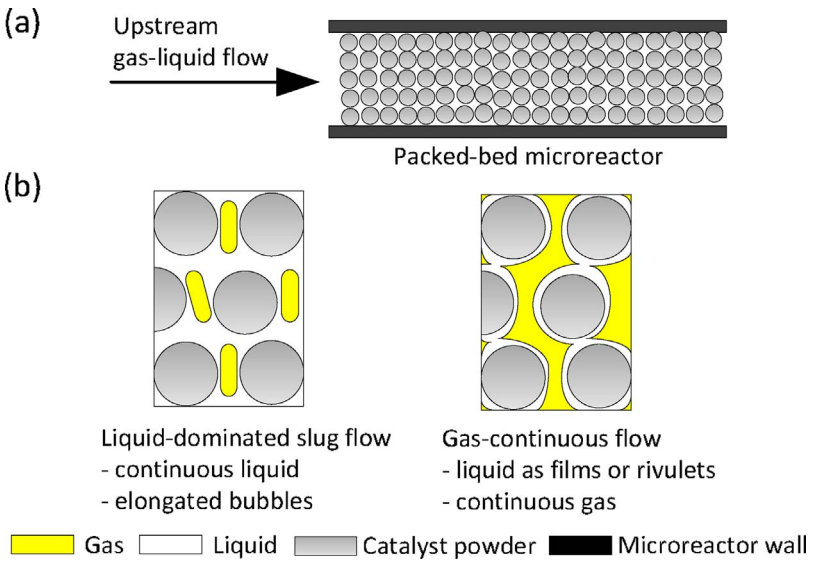


Fig. 3. Packed-bed microreactors. (a) Schematics of the microreactor geometry (in the case of solid-catalyzed gas-liquid reaction). (b) Two major gas-liquid flow patterns over the catalyst bed according to the literature [34].

2.2.2. Transport characteristics

Gas-liquid flow pattern in packed-bed microreactors, although resembling to some extent those in conventional packed-bed reactors with particle size on the order of millimeters, exhibits peculiar characteristics due to the dominance of surface forces over gravitational forces at micrometer scale. A representative study has demonstrated very recently that two major gas-liquid flow patterns could be observed in packed-bed microreactors [34]:

- Liquid-dominated slug flow (Fig. 3a): liquid covers the particle interstitial voids and the majority of the catalyst bed, with gas travelling in the form of elongated bubbles possibly subject to distortion during flow passage through irregular voids. This flow pattern dominates at relatively low superficial gas velocity and high superficial liquid velocity.
- Gas-continuous flow (Fig. 3b): this flow pattern is favored at relatively high superficial gas velocity and low superficial liquid velocity. There is a presence of a continuous gas phase, while at moderate gas-liquid flow ratios liquid presents as a more uniformly distributed liquid film surrounding catalyst particles (i.e., catalyst being fully wetted) and at elevated gas-liquid flow ratios liquid film translates into rivulets leaving some parts of catalyst particles exposed directly to gas (i.e., catalyst being partially wetted).

A transitional flow pattern, segregated flow, exists in between the two major flow patterns mentioned above, featuring a constant occupancy of the catalyst bed by gas and liquid separately. Here, liquid-dominated slug flow is analogous to the induced pulsing flow in conventional packed-bed reactors, and gas-continuous flow (induced by surface forces) is analogous to trickle flow (but induced by gravitational forces) [34].

The transition from high-interaction zone (i.e., liquid-dominated slug flow) to low-interaction zone (i.e., gas-continuous flow) was found to take place generally at a much smaller liquid to gas flow ratio than that observed in conventional packed-bed reactors [34,96,97], due to the dominance of surface forces in packed-bed microreactors. This transition further depends on many factors such as the upstream gas-liquid flow pattern before the packed bed, catalyst particle sizes and shape, method of packing, microchannel diameter to particle diameter ratio, which is currently an emerging topic of study [98].

Most of the existing gas-liquid-solid reactions explored in packed-bed microreactors (as listed in Table 2) were probably carried out under liquid-dominated slug flow pattern (Fig. 3a), since gas-liquid slug flow was usually observed before the catalyst bed [35,87–93]. Noteworthy, a recent work highlighted reaction performance under both liquid-dominated slug flow and gas-continuous flow patterns [34].

The preference of packed-bed microreactors over conventional packed-bed reactors for chemical synthesis stems from firstly the superior heat transfer performance that is easily accessible at micrometer scale. Large packed-bed reactors with particle size usually at a few millimeters tend to suffer from the insufficient heat transfer area and poor radial heat transfer, rendering difficulties in its operation with a highly exothermic reaction (e.g., in preventing the hot spot formation that may cause unfavorable reaction performance or even explosion risks). In contrast, the internal channel diameter of packed-bed microreactors is usually below 1 mm and the size of the loaded catalyst particles usually in a range of 10–100 μm (Table 2), which ensures an exceptionally high heat transfer area between fluids and reactor walls or catalysts (e.g., on the order of 10,000 m^2/m^3), as well as a fast radial heat transfer due to narrowed microchannel cross-section. Secondly, substantially improved gas-liquid(-solid) mass transfer rates beneficial for operating a reaction under intrinsic kinetic control are also (largely) available in packed-bed microreactors. The overall volumetric gas-liquid mass transfer coefficients on the order of 1–10 s^{-1} in packed-bed microreactors have been reported under reaction conditions [92,96], which are at least 1 or 2 orders of magnitude higher than those achievable in conventional packed-bed reactors. This substantial mass transfer enhancement is very critical for improving the rate of gas-liquid-solid reactions. As an example, liquid-phase hydrogenation and oxidation reactions in conventional packed-bed reactors are often limited by mass transfer of gas to liquid, given very low gas solubility in normal solvents and thereby the reaction is usually operated under high pressure conditions leading to safety risks. Thus, packed-bed microreactors hold great promises for efficiently carrying out highly exothermic and/or fast gas-liquid reactions under relatively mild reaction conditions.

For liquid-liquid flow in continuous flow reactors including microreactors with packed (catalyst) particles, there are very limited studies [65,94,99,100]. Usually, reactions under investigation were reported with the presence of an upstream liquid-liquid slug flow before the catalyst bed. Thus, the actual flow pattern in the packed bed might be somewhat similar to liquid-dominated slug flow (Fig. 3a), the inner characteristics of which still need to be researched in detail. Under such continuous liquid-liquid processing in packed-bed microreactors, an improvement in the reaction performance is anticipated, given e.g. the large interfacial area created to facilitate mass transfer and reaction at interfaces.

As compared with wall-coated microreactors, packed-bed

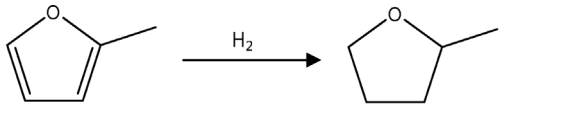
microreactors usually present a larger pressure drop due to the accommodation of fine catalyst particles, more complex fluid dynamics, less controlled catalyst wetting, and less superior heat transfer performance within the catalyst. However, the latter microreactor concept eliminates the need for the development of dedicated coating methods, allows a much wider range of catalyst and reaction choices, and can easily provide sufficient (active) catalyst amount that is required for the interested reaction.

2.2.3. Selected reaction examples

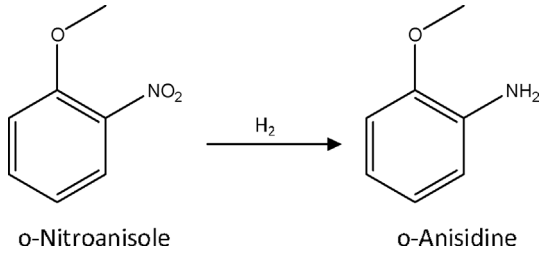
2.2.3.1. Selective hydrogenation. The catalytic upgrading of bio-oils (e.g., obtained from pyrolysis of renewable lignocellulosic biomass) via hydrodeoxygenation in the presence of H_2 and heterogeneous catalysts is a promising valorization strategy towards their promising uses as transportation biofuels [101]. Microreactors represent an efficient equipment for such high pressure hydrogenation reactions given its inherent safety and improved heat/mass transfer. A preliminary study following this line has been demonstrated [86]. A model bio-oil compound, 2-methylfuran, has been hydrogenated to 2-methyltetrahydrofuran (an approved gasoline additive) under solvent-free conditions in a silicon-Pyrex microreactor chip where a commercial 5 wt% Pd/C catalyst was packed in its four main reaction microchannels (Scheme 11; Table 2, entry 1). Under a hydrogen pressure of 45 bar, 2-methylfuran conversion in the microreactor increased to ca. 45% upon increasing temperature to 160 °C, with an exclusive formation of 2-methyltetrahydrofuran. It seems that the small packed-bed microreactor geometry and the applied high pressure significantly improved gas-liquid-solid mass transfer, and thus allowed to operate the reaction under intrinsic kinetic control especially at low temperatures or conversions.

Catalytic hydrogenation of o-nitroanisole over solid catalysts to produce o-anisidine is an important route used in the pharmaceutical and fine chemical industries, e.g., towards obtaining napthol pigments and dyes [87]. Packed-bed microreactors have been studied as an alternative to the conventional semi-batch slurry reactors for this reaction [87,88]. The reaction was tested in a stainless steel capillary microreactor packed with commercial 2 wt% Pd/zeolite catalyst (Scheme 12; Table 2, entry 2). A cold-flow test suggested the existence of a slug flow-like flow pattern under reaction conditions, i.e., an upstream gas-liquid slug flow in an otherwise empty microreactor was distorted by the presence of catalyst particles with the slug boundary being broken up. The reaction conversion was found to increase significantly with temperature while the selectivity towards o-anisidine always remained close to 100%, suggesting that the reaction may be controlled by intrinsic kinetics due to negligible heat/mass transfer resistances over a wide range of operating conditions. This facilitated a reliable kinetic modelling for reaction performance optimization and for helping the elucidation of reaction mechanisms. Moreover, the positive effect of operation with high hydrogen pressure on the reaction rate enhancement was shown, as a result of the increased concentration of dissolved hydrogen [87].

A similar stainless steel capillary microreactor packed with commercial 1 wt% Pd/SiO_2 catalyst has been further studied for hydrogenation of 2-ethylanthraquinone to 2-ethylanthrahydroquinone (a first step in the commercial Reidl–Pfleiderer process for H_2O_2 production), under a hydrogen pressure of ca. 7 bar and reaction temperature up to 80 °C (Scheme 13; Table 2, entry 3) [89]. The experimental results



Scheme 11. Hydrogenation of 2-methylfuran to 2-methyltetrahydrofuran.

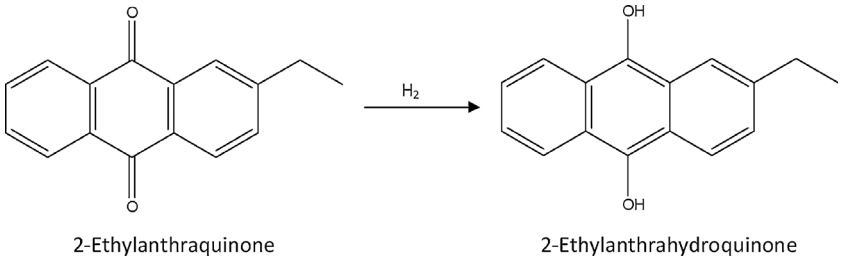


Scheme 12. Hydrogenation of o-nitroanisole to o-anisidine.

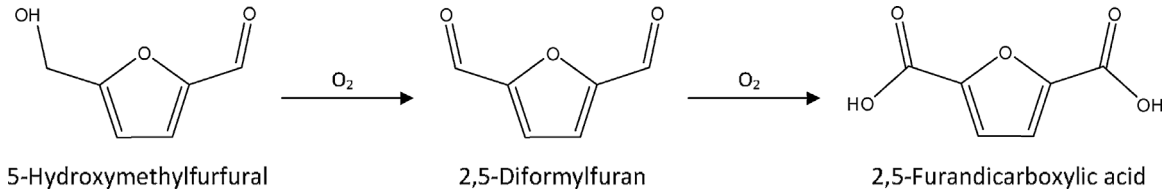
indicated that the gas-liquid(-solid) mass transfer resistance in the microreactor tended to be important at high temperature levels, given the conversion increase with temperature became smaller. Nevertheless, the space time yield in the current microreactor was still 30–50 times larger than those obtained in a conventional packed-bed reactor (with a reactor diameter of 5.4 cm) and a commercial slurry reactor under similar operation conditions over Pd catalysts. This comparison clearly illustrates the potential of microreactors for use in hydrogenation of anthraquinone which is likely under severe mass transfer control in conventional reactors.

2.2.3.2. Selective aerobic oxidation. Solvent-free oxidation of benzyl alcohol to produce benzaldehyde has been performed in a silicon-glass microreactor of which the serpentine reaction microchannel was packed with 0.05 wt% Au-0.95 wt% Pd/TiO_2 catalyst (Fig. 1c), under 1 bar oxygen pressure at reactor outlet and 120 °C (Scheme 7; Table 2, entry 4) [34]. An increase in both the conversion of benzyl alcohol and selectivity towards benzaldehyde was found with an increase of gas flow rate at which the flow pattern changed from liquid-dominated slug flow (Fig. 3a), to the transitional segregated flow, and further on to gas-continuous flow (with fully wetted catalysts) (Fig. 3b). Such conversion increase with gas flow rate was mainly due to enhanced gas-liquid mass transfer (i.e., increased gas-liquid interfacial area and decreased liquid film thickness) offering high oxygen availability to the catalyst surface for an increased conversion. The large oxygen availability further enhanced the direct catalytic oxidation pathway producing exclusively benzaldehyde, thus increasing its selectivity (i.e., the disproportionation pathway producing equal amount of benzaldehyde and toluene was less favored). However, benzyl alcohol conversion tended to drop significantly at very high gas flow rates under gas-continuous flow pattern, due to the inefficient use of catalyst (being partially wetted) causing a significant liquid-solid mass transfer resistance as well as benzyl alcohol evaporation. Thus, gas-continuous flow under fully or sufficiently wetted catalyst conditions (Fig. 3b) was a favorable flow pattern for the current microreactor operation, wherein a conversion of benzyl alcohol above 90% and selectivity to benzaldehyde over 80% could be achieved at a contact time (defined as the catalyst weight over alcohol mass flow rate) of 76 $g_{catalyst}$ s/$g_{alcohol}$. In contrast, the same reaction in a batch glass stirred reactor only yielded a conversion of 75.6% and selectivity to benzaldehyde of 73.9% at a contact time of 38 $g_{catalyst}$ s/$g_{alcohol}$ (defined as the catalyst weight multiplied by batch reaction time over alcohol mass), clearly showing the intensification potential of packed-bed microreactors. The work here has highlighted the importance of ensuring a favorable gas-liquid-solid contacting pattern in the packed-bed microreactor for a desired reaction performance, which is not a trivial task given complex hydrodynamics and somewhat uncontrolled catalyst wetting therein.

The use of selective aerobic oxidation of benzyl alcohol as a benchmark reaction has been further demonstrated in a Teflon capillary microreactor filled with commercial silica-immobilized 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO) catalyst, in combination with HNO_3 as a co-oxidant [90]. At a temperature of 55 °C, oxygen pressure of 5 bar and in the presence of 5 mol% HNO_3, a 98% conversion of benzyl alcohol (intake: 0.5 M in 1,2-dichloroethane) with 99% aldehyde



Scheme 13. Hydrogenation of 2-ethylanthraquinone to 2-ethylanthrahydroquinone.



Scheme 14. Aerobic oxidation of 5-hydroxymethylfurfural to 2,5-diformylfuran and 2,5-furandicarboxylic acid.

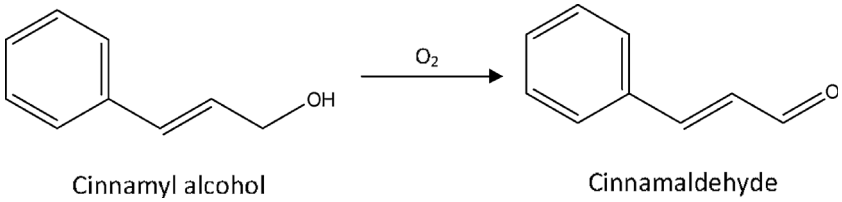
selectivity could be achieved at 0.5 min residence time in the microreactor that was probably operated under liquid-dominated slug flow pattern (Scheme 7; Table 2, entry 5). No catalyst decomposition was noticed during 8 h on stream. Moreover, the same microreactor and catalyst system exhibited high efficiency in the aerobic oxidation of 5-hydroxymethylfurfural (HMF; a bio-based platform chemical) to promising polymer building blocks including 2,5-diformylfuran (DFF) and 2,5-furandicarboxylic acid (Scheme 14; Table 2, entry 5). At a residence time of 2 min, a 97% conversion of HMF (intake: 0.41 M in 1,2-dichloroethane) with 98% selectivity towards DFF could be achieved and FDCA was produced at longer residence times, the other operational conditions being the same as in the case of benzyl alcohol. The use of microreactors has shown to provide orders-of-magnitude higher space time yields than comparable batch reactor systems and meanwhile led to a reduction in the use of co-oxidants, which thus added to the cost and environmental benefits of continuous flow processes.

Heterogeneously catalyzed oxidation of cinnamyl alcohol to cinnamaldehyde (with important uses in organic synthesis and applications in the food and perfume industries) has been studied recently in a PTFE capillary microreactor packed with self-prepared 1 wt% bimetallic Au-Pd/TiO_2 catalyst (Scheme 15; Table 2, entry 6) [91]. A gas-liquid slug flow was generated before entering the microreactor. However, catalyst deactivation was noticed at 120 °C and a pure oxygen pressure of 4 bar: alcohol conversion decreased from initially 58% to 33% after 7 h on stream, albeit a stable selectivity to cinnamaldehyde at around 61%. This deactivation seemed to be caused by Pd leaching (possibly accelerated at high oxygen concentrations) and poisoning of catalyst surface by adsorbed oxygen or other species formed in the reaction, thereby posing a challenge for catalyst improvement. Notwithstanding, a clear advantage was seen in the utilization of continuous flow processing and mass transfer intensification in packed-bed microreactors for a faster and more reliable assessment of catalyst stability when compared with conventional batch reactor studies.

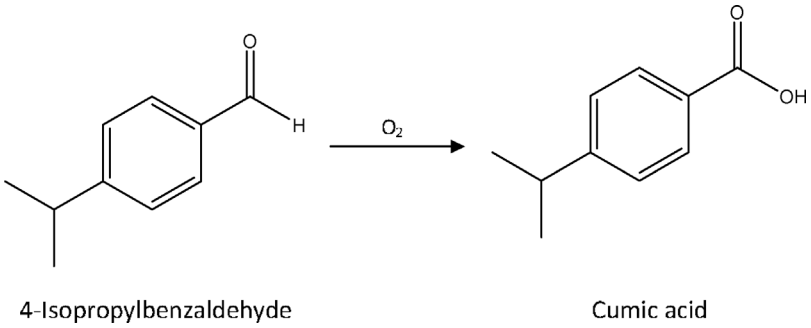
The oxidation of 4-isopropylbenzaldehyde to cumic acid (an important intermediate for pharmaceutical synthesis) has been reported in a single-channel silicon-Pyrex microreactor that was loaded with commercial 5 wt% Pt/Al_2O_3 catalyst particles (Scheme 16) [86]. Using an inlet concentration of 1.5 M 4-isopropylbenzaldehyde (in n-butyl acetate), a reaction temperature of 90 °C and 2 bar pure oxygen pressure, 95% yield of cumic acid could be achieved within a few seconds (Table 2, entry 7). Such promising results were ascribed to the precise residence time control combined with an efficient heat removal under continuous gas-liquid processing. Thus, the hot spot formation and/or the unwanted secondary oxidation to e.g. combustion products were largely suppressed. Moreover, the reaction appeared much faster in the current microreactor than operation in a semi-bath slurry reactor in which hours were needed to complete.

2.2.3.3. Direct synthesis of hydrogen peroxide. The direct combination of H_2 and O_2 to produce H_2O_2 over heterogeneous catalysts (Scheme 8) as an atom efficient and environmentally benign process has also been demonstrated successfully in packed-bed microreactors [35,92,93,102]. This microreactor configuration might be more effective in terms of safely handling the explosive H_2-O_2 mixtures than wall-coated microreactors, given that the closely packed micrometer-sized catalyst particles could effectively minimize void spaces and thus prevent flame ignition and explosion.

A 10-channel silicon-Pyrex microreactor chip packed with commercial 5 wt% Pd/C catalyst has been employed in an earlier stage to produce 0.2 wt% H_2O_2 from H_2-O_2 mixtures in the explosive regime, and under pressures of 20–30 bar and ambient temperature (Table 2, entry 8) [92]. The flow pattern in the microreactor was likely liquid-dominated slug flow. A nearly 100% selectivity towards H_2O_2 could be achieved at low H_2 conversion (< 5%) when using a high bromide concentration in the aqueous solution to suppress peroxide decomposition. The use of carbon support herein allowed a good catalyst wetting and thus reasonable selectivity to peroxide. In contrast, dry voids between catalyst particles were found in the case of Al_2O_3 and SiO_2 supports favorable for complete oxidation. A further increase of H_2O_2 concentration to 0.6 wt% was achieved by operating two microeactors in series over Pd/C catalysts in the presence of an improved gas-liquid distribution in the second reactor, suggesting a possibility of increased epoxide production by further optimizing reactor design and operation. However, palladium leaching was noticed under the



Scheme 15. Oxidation of cinnamyl alcohol to cinnamaldehyde.



Scheme 16. Oxidation of 4-isopropylbenzaldehyde to cumic acid.

involved acidic and oxidative reaction conditions, although it could be largely reduced by operation at high hydrogen-to-oxygen ratios.

Over 3 wt% H_2O_2 concentration has been later obtained in a single-channel glass microreactor chip packed with commercial 5 wt% Pd/Al_2O_3 catalyst, under ambient temperature and H_2-O_2 mixture pressure up to 20 bar (Table 2; entry 9) [93]. This productivity increase was ascribed to an improved gas-liquid distribution over the catalyst bed (i.e., by differentiating the sizes of gas- and liquid-side inlet channels to suppress cross-talk between them) and enhanced catalyst activity by liquid-phase reduction treatment during catalyst preparation. Although a stable continuous operation of the microreactor system up to 1 week was achieved, a palladium leaching was likely present leading to peroxide concentration decrease over time.

A significant increase of H_2O_2 concentration to ca. 10 wt% (closer to industrial needs) was shown possible by a combination of two single-channel glass microreactor chips (Fig. 1d) for long residence time operation, each being packed with self-made monometallic (Pd) or bimetallic (Pd-Au) catalyst with TiO_2 as support (Table 2, entry 10) [35]. The direct synthesis was performed under ambient temperature and 10 bar H_2-O_2 mixture pressure at the microreactor outlet. Such high productivity was thought to be a result of improved gas-liquid contacting over the catalyst bed, enhanced heat/mass transfer rates in microreactors, and a proper catalyst choice (e.g., TiO_2 supported Pd or Pd-Au catalyst could keep higher selectivity to peroxide than Pd/Al_2O_3 catalyst).

2.2.3.4. Biodiesel synthesis. Biodiesel (especially when derived from non-edible renewable feedstocks) represents an environmentally friendly fuel [18]. Currently, its industrial production is mainly via homogeneous base-catalyzed transesterification reaction between edible oils and C1-C2 alcohols in conventional reactors. The use of heterogeneous catalysts is viewed as a greener approach to uplift the current industrial route, facilitating simple catalyst separation/reuse and subsequent product purification [18]. The presence of two immiscible phases in the reaction usually incurs mass transfer limitation, therefore continuous flow processing in microreactors has been explored over recent years as an efficient production unit for biodiesel synthesis, but mainly using homogeneous catalysts [103–105].

Biodiesel synthesis via transesterification of palm oil with methanol over solid CaO catalyst packed in a plate-type microreactor made of aluminum alloy has been demonstrated (Scheme 17; Table 2, entry 11) [94]. By using 2-propanol as a co-solvent to improve the solubility of oil and methanol, over 98% yield of methyl esters could be obtained at a residence time of ca. 6.5 min, with a purity of 99%. Compared with the literature results obtained in conventional batch slurry or packed-bed reactors, biodiesel productivity in the microreactor was about 2–10 times higher and calcium leaching therein was relatively lower. These results, although preliminary, corroborate the great potential of microreactors combined with solid catalysts in more efficient and greener biodiesel synthesis.

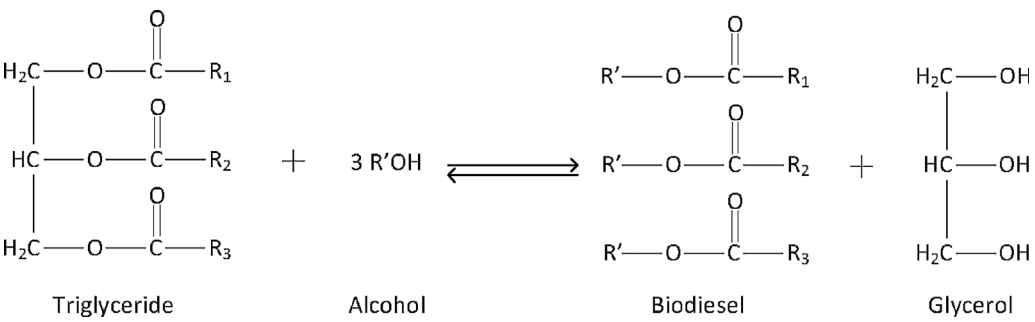
2.2.4. Opportunities and challenges ahead

Packed-bed microreactors allow a fast identification of intensification potential of continuous microflow processing mainly due to an easy incorporation of commercial or conventionally prepared catalysts, as demonstrated in various solid-catalyzed biphasic reactions (cf. Table 2). While gas-liquid-solid hydrogenation and oxidation reactions are currently a primary focus [34,35,86–93], emerging application areas are to be found especially in liquid-liquid-solid catalytic systems (e.g., oxidation using H_2O_2 [52], transesterification [94]). The use of solid catalysts as an increasingly popular choice in continuous flow chemistry will naturally direct more researches in packed-bed microreactors as well [14,16,22]. For a maximized reaction performance, the design and operation of packed-bed microreactor needs to be optimized in order to generate a favorable gas-liquid-solid contacting pattern preferably without a large pressure drop penalty, which represents a significant challenge in view of less controlled multiphase hydrodynamics and catalyst wetting therein compared with wall-coated microreactors. Long-term catalyst stability (e.g., leaching and catalyst poisoning) is another challenge to tackle [91–94].

2.3. Miscellaneous microreactors

Apart from wall-coated and packed-bed microreactors highlighted in this review as two common microreactor types for carrying out solid-catalyzed multiphase (gas-liquid and liquid-liquid) reactions, some other microreactor concepts have been explored meanwhile and are briefly summarized hereafter.

Falling film microreactors are another reactor type suitable for such



Scheme 17. Transesterification of triglyceride with alcohol for biodiesel synthesis.

purposes, which feature the use of gravitational forces to generate very thin liquid films (e.g., below 100 μm) inside a plurality of microchannels [106]. By coating solid catalysts on the bottom of microchannels, an efficient gas-liquid-solid contacting can be realized for intensifying reactions such as hydrogenation [107,108] and immobilized enzyme-catalyzed biocatalytic oxidation [109], with the additional advantage of an easy gas-liquid separation.

A smart processing principle has been conceived using membrane microreactors in which gas and liquid are separated by a membrane that provides a controlled and selective delivery of reactive gases (e.g., H_2, O_2) into the liquid substrate (thereby improving safety), where the catalyst can be in a first place incorporated as coatings on the membrane [110,111]. Recently, an increasing attention in this area has been paid to the use of tube-in-tube membrane microreactors. In the latter case, the configuration comprises an outer capillary and an inner capillary made of a (highly) permeable membrane material such as AF-2400 (a copolymer of tetrafluoroethene and perfluorodimethyldioxolane) as interface between gas and liquid phases, where the catalyst particles can be packed in the inner tube or shell side [112–115]. The promising uses of such membrane microreactors have been particularly demonstrated in selective hydrogenation of nitrobenzene [111], olefin metathesis [112], selective oxidation of benzyl alcohol [113,114] and HMF [115].

Last but not least, solid catalysts can be combined with microreactor operations in various forms other than just as packed powder particles or wall coatings. For example, they can be functionalized onto structured monoliths that are subsequently filled into microreactors [21,22], or can be directly carried with gas-liquid/liquid-liquid flow to realize continuous gas-liquid-slurry or liquid-liquid-slurry operation [116–118]. All these microreactor concepts will create vast possibilities towards a more efficient chemical synthesis.

3. Concluding remarks and outlook

Researches on heterogeneous catalysis in conjunction with multiphase flow processing in microreactors have been on the rapid rise, given the huge potential of this approach towards the development of an efficient and sustainable chemical synthesis particular relevant to fine chemicals and pharmaceutical industries. Solid catalysts have been incorporated into capillary- and chip-based microreactors in the form of either catalytic wall coatings or powder particles as covered in this review. Thus developed wall-coated and packed-bed microreactors have shown their great effectiveness in a variety of multiphase reactions including among others, gas-liquid selective hydrogenation and aerobic oxidation, direct synthesis of H_2O_2, biphasic epoxidation with H_2O_2, and transesterification. The precise two-phase flow manipulation, substantial transport intensification and inherent safety in microreactors largely allow to operate these catalytic reactions either at ease or at an exceptionally high reaction rate and productivity that are usually difficult to realize in conventional reactors. The green aspects of these chemical syntheses have been well addressed by a switch to the use of active and selective heterogeneous catalysts and environmentally friendly reagents (e.g., H_2O_2 and O_2 as clean oxidants, renewable feedstock or bio-based platform chemicals such as plant oil and 5-hydroxymethylfurfural), combined with high process efficiency made available by multiphase flow processing in microreactors.

The majority of the current application examples are centered on gas-liquid-solid systems, with only a few examples demonstrated for liquid-liquid-solid systems. In the former case, it is further necessary to explore a promising application potential in green and/or bio-based chemicals and material synthesis (e.g., hydrogen and oxidation being important strategies in the valorization of biomass and its derivatives). More researches should be directed towards chemical transformations in the presence of other reactive gases (e.g., CO, CO_2) as well [23]. In the latter case, additional researches are particularly welcome, given the relevance to important application areas such as solid-catalyzed biodiesel synthesis and aqueous-organic oxidative transformations with H_2O_2 as highlighted in this review. Wall-coated and packed-bed microreactors as two promising types of catalytic microreactors for intensifying multiphase reactions still have some way to go before their promising application in practice. For wall-coated microreactors, fundamental knowledge on the preparation-structure-activity relationship for various catalytic coatings needs to be well established to guide the catalyst and process design. Especially, the coating formulation and procedure have to be optimized (e.g., to suppress a possible catalyst leaching and ensure a good catalyst adhesion to the wall). The durability of catalytic wall coatings has to be further verified under industrially relevant reaction conditions, although some laboratory tests have showcased their stability over weeks [32,38–40,42]. A further room for intensification also exists particular by switching to operation under elevated gas pressures or solvent-free conditions. Ongoing researches should be paid specifically to packed-bed microreactors as an increasingly popular choice in continuous flow chemistry. It is still not very clear how to design and operate such type of microreactors properly in order to ensure a well-controlled multiphase hydrodynamics and wetting over the packed catalyst bed for a maximized reactor performance without incurring a large pressure drop in the system [98]. A knowledge gap exists on the underlying interplay between (gas-liquid-solid or liquid-liquid-solid) transport and catalytic reaction on the micrometer scale. Improvement of long-term catalyst activity and stability remains as another non-trivial task (e.g., under acidic and oxidative conditions). Regarding the production capacity increase to meet the industrial requirement, the existing concepts for numbering up gas-liquid or liquid-liquid microreactors can be in principle extended for further use herein, as have been demonstrated to some extent [119,120]. However, the modularity, robustness, flexibility and cost effectiveness of these concepts need to be further examined. An engineering design challenge is also present when a huge number of microreactor channels (e.g., thousands) are involved, especially in terms of uniform multiphase flow distribution and identical catalyst performance in each microchannel. In order to well address all the above-mentioned opportunities and challenges, it is envisaged that a joint effort from both academia and industry is required, preferably using a combined green chemistry and engineering approach.

Acknowledgement

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